REMARKS

Applicants thank the Examiner for the telephonic discussion on August 13, 2004, where Applicants elected to prosecute the species of "hypertension."

Claims 1-20 and 25-57 are pending. Claims 29, 30, 43, 44 and 46-49 are withdrawn from consideration as they allegedly read on non-elected species. Applicants amend claims 1, 25, 31, 40, 45, and 57 to recite the elected species of "hypertension" and to more clearly define P-selectin ligand activity. Applicants cancel claim 28 without prejudice. Exemplary support for amendments to the claims is in the specification at least at page 6, lines 1-26, for example.

Claims 1-20, 25-27, 31-40, 45 and 50-57 will remain pending after the entry of this amendment. Applicants believe that this amendment places the claims in condition for allowance and request the same.

Enablement Rejection under 35 U.S.C. §112, First Paragraph

Claims 1-20, 25-28, 31-42, 45 and 50-57 have been rejected as allegedly not enabled by the specification as-filed. Specifically, the Examiner acknowledges that the specification is enabling for PSGL-1 and fragments thereof which inhibit interaction of P-selectin or E-selectin and PSGL by inhibiting interaction of P-selectin or E-selectin expressing endothelial cells and activated platelet with PSGL expressing leukocytes, including P-selectin binding domains and fragments. (9/9/04 Office Action at page 2). The Examiner, however, alleges that the specification does not provide enablement for any PSGL-1 protein or a fragment thereof, including any PSGL-1 protein or fragment thereof having a P-selectin ligand activity. *Id.*

Without acquiescing to this rejection, however in an effort to further prosecution, Applicants have amended the claims to recite specific P-selectin ligand activities discussed in the specification, as suggested by the Examiner. Accordingly, Applicants request that this rejection be withdrawn.

Anticipation Rejection under 35 U.S.C. §102(e) over Cummings

Claims 1-4, 8-13, 16-18, 25-28, 45-47, 50-53 and 57 have been rejected as allegedly being anticipated under 35 U.S.C. § 102(e) by U.S. Patent No. 5,464,778 to Cummings et al. ("*Cummings*"). The Examiner acknowledges that *Cummings* is silent about hypertension. The Examiner, however, alleges that the persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in *Cummings* would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments as taught by *Cummings*. (9/9/04 Office Action at page 4).

Applicants disagree with the Examiner's understanding of *Cummings*. First, to serve as an anticipation rejection, a reference must disclose each and every limitation of the claimed invention. Further, to serve as an anticipation reference in an inherency rejection, the reference must make clear that the missing descriptive matter is necessarily present in the thing described in the reference. *Schering Corporation v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1376 (Fed. Cir. 2003).

Instant claims are directed to a method of treating or inhibiting thrombosis in a subject by administering an effective amount of a PSGL-1 protein to the subject, where the subject has hypertension.

The Examiner has cited *Cummings* for the proposition that hypertension is necessarily associated with the conditions discussed in *Cummings*, and therefore, administration of PSGL-1 to treat conditions recited in *Cummings* would necessarily treat hypertension and consequently thrombosis. Applying the above discussed legal precedent to *Cummings*, Applicants note that *Cummings* fails to make clear that hypertension is necessarily associated with the conditions discussed therein, as alleged by the Examiner.

Cummings describes a glycoprotein ligand for P-selectin. *Cummings* further discusses that P-selectin has several functions relating to leukocyte adherence, inflammation, tumor metastasis, and coagulation, and speculates on the use of a P-selectin ligand protein to modulate these conditions. *See* column 18, lines 34-39. *Cummings*, however, fails to teach or suggest that hypertension would necessarily be associated with any of the conditions discussed therein, and this seems to be Examiner's own hypothesis.

Applicants note that not only does *Cummings* fail to specifically comment on the role of P-selectin or a PSGL-1 protein in thrombosis, thereby providing no motivation to use a PSGL-1 protein for treating or inhibiting thrombosis in a subject, but *Cummings* also fails to teach or suggest that hypertension is necessarily associated with the various acute and chronic conditions disclosed in *Cummings*. Therefore, based on *Cummings*, one of ordinary skill in the art would not be motivated to use PSGL-1 for treating either hypertension or thrombosis, let alone treating thrombosis associated with hypertension.

In view of the foregoing, Applicants respectfully submit that *Cummings* fails to anticipate the claimed invention, either explicitly or inherently and request that this rejection be withdrawn.

Anticipation Rejection under 35 U.S.C. §102(e) over Larsen

Claims 1-5, 7-18, 25-28, 45-47 and 50-57 have been rejected as allegedly being anticipated under 35 U.S.C. § 102(e) over U.S. Patent No. 5,840,679 to Larsen ("*Larsen*"). As in the case of *Cummings*, the Examiner again alleges that the persistently high arterial blood pressure or hypertension associated with the various acute and chronic conditions disclosed in *Larsen* would have been inherently inhibited or treated by the administration of inhibitory PSGL-1 and fragments taught by *Larsen*. (9/9/04 Office Action at page 5).

As discussed above, the claimed invention is directed to the use of PSGL protein to treat or inhibit thrombosis in a subject with hypertension. Contrary to the Examiner's understanding of *Larsen*, *Larsen* fails to make clear that hypertension would be necessarily associated with the conditions discussed therein.

Larsen speculates on the use of an "isolated" P-selectin ligand protein in treating conditions characterized by P-selectin mediated intercellular adhesion including myocardial infarction, bacterial or viral infection, metastatic conditions etc. *See* column 15, lines 50-66. The Examiner is alleging that PSGL-1 administered for treating the conditions recited in *Larsen*, would treat hypertension, and consequently thrombosis. However, this seems to be Examiner's own hypothesis as *Larsen* does not teach or suggest that hypertension is even associated with any of the conditions discussed in *Larsen*.

Accordingly, based on *Larsen*, one of ordinary skill in the art could not draw an inference that administration of PSGL-1 to treat conditions discussed in *Larsen* would treat either hypertension or thrombosis, let alone thrombosis associated with hypertension.

In view of the foregoing, Applicants submit that *Larsen* fails to anticipate claimed invention, either explicitly or inherently.

Obviousness Rejection over Cummings and Larsen in view of Blann, Araneo and DeFrees

Claims 1-20, 25-28, 31-42, 45 and 50-57 have been rejected under 35 U.S.C. § 103 as allegedly being obvious over *Cummings* and *Larsen* further in view of Blann et al. (J. Human Hypertension 11:607-609 (1997)) ("*Blann*"), U.S. Patent No. 6,150348 to Araneo et al. ("*Araneo*") and U.S. Patent No. 5,604,207 to DeFrees et al. ("*DeFrees*"). In particular, the Examiner acknowledges that neither *Cummings* nor *Larsen* discloses inhibiting hypertension and deep vein thrombosis by inhibiting P-selectin and PSGL-1 interactions per se, *Blann*, *Araneo* and *DeFrees* all teach the role of such interactions in various thrombotic conditions, including hypertension and deep vein thrombosis at the time the invention was made. (9/9/04 Office Action at page 7).

Applicants respectfully disagree. A proper *prima facie* obviousness rejection requires that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. Also,

see *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1443 (Fed. Cir. 1991) (the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure).

The Examiner appears to contend that administration of PSGL-1 to treat conditions that are recited in *Larsen* and *Cummings* would inherently treat hypertension, and consequently thrombosis.

As discussed above, *Cummings* and *Larsen*, both speculate using PSGL for treating various conditions. However, not only do both *Cummings* and *Larsen* fail to teach or suggest using a PSGL-1 protein for treating or inhibiting thrombosis, but they provide no teaching or suggestion that hypertension is associated with any of the conditions discussed in *Cummings* or *Larsen*, which seems to be Examiner's own hypothesis.

None of *Blann*, *Araneo* and *DeFrees* cure the deficiencies of *Cummings* and *Larsen*. First, none of them teach or suggest that hypertension is necessarily associated with the conditions discussed in *Cummings* and/or *Larsen*. Second, Applicants note that each of *Blann*, *Araneo* and *DeFrees* discuss compounds other than a PSGL-1 protein for treating conditions other than thrombosis in a subject where the subject has hypertension, as recited by the instant claims. Applicants discuss the teachings of each of these references below.

Blann fails to teach or suggest that hypertension is necessarily associated with any of the conditions discussed in *Cummings* and/or *Larsen*. *Blann* discusses that levels of soluble P-selectin are raised in hypertension. *See* Abstract. Applicants note that *Blann* merely speculates that therapeutic strategies aimed at reducing platelet

activity may be beneficial (*see* page 608, column 2). However, *Blann* fails to teach or suggest that a PSGL-1 protein would be beneficial at reducing platelet activity. *Blann* in fact teaches away from the use of a PSGL-1 protein, as it teaches using compounds such as aspirin for reducing hypertension. *Id.* Further, it is not clear from *Blann* whether rise in the levels of soluble P-selectin in patients with hypertension is a cause or consequence of hypertension—thus, any relationship between P-selectin and hypertension is not explained. Accordingly, based on *Blann*, one of ordinary skill in the art would have no motivation to specifically use a PSGL-1 protein for treating or inhibiting hypertension, let along treating or inhibiting thrombosis in a subject with hypertension. At best, *Blann* might provide the motivation to use a compound that is similar to aspirin.

Like *Blann*, *Araneo* also fails to teach or suggest that hypertension is necessarily associated with any of the conditions discussed in *Cummings* and/or *Larsen*. *Araneo* discusses methods of preventing or reducing effects of ischemia and certain other conditions including pulmonary hypertension, by administering a dehydroepiandrosterone (DHEA) derivative. *See* Abstract. *Araneo* discusses at column 17, lines 59-64, that administration of a DHEA derivative for reducing adherence of blood cells and platelets to endothelial cells reduces the expression of P-selectin. *Araneo*, however, fails to provide any discussion of a relationship between hypertension and P-selectin, let alone hypertension and PSGL-1. Applicants note that not only does *Araneo* provide no motivation to use a PSGL-1 protein in its methods, but *Araneo* fails to teach or suggest treating thrombosis in a subject with hypertension. Further, an observation that DHEA reduces expression of P-selectin provides no motivation to use

a PSGL-1 protein with one or more activities recited in the amended claims, none of which specifically require reducing expression of P-selectin.

DeFrees also does not teach or suggest that hypertension is necessarily associated with any of the conditions discussed in *Cummings* and/or *Larsen*. *DeFrees* provides compounds which are analogues of sialyl Le^X. *See* Abstract. *DeFrees* further contemplates that such compounds may be used for the treatment of various disorders including deep vein thrombosis. *See* column 45, lines 7-15. As in the case of *Araneo*, Applicants again submit that not only does *DeFrees* fail to specifically teach or suggest using a PSGL-1 protein in any treatment methods, but the alleged treatment of deep vein thrombosis discussed in *DeFrees* using the sialyl Le^X analogues fails to imply or inherently disclose treating or inhibiting thrombosis or deep vein thrombosis in a subject with hypertension, as *DeFrees* fails to teach or suggest any relationship between P-selectin or PSGL-1 and hypertension.

In view of the foregoing, Applicants submit that none of *Blann*, *Araneo* and *DeFrees* cure the deficiencies of *Cummings* and *Larsen* and respectfully request that this rejection be withdrawn.

Obviousness Rejection under 35 U.S.C. § 103(a) over Cummings and Larsen in further view of Blann, Araneo and DeFrees and as evidenced by Maugeri and Johnson.

Claim 27 has been rejected as allegedly being obvious over *Cummings* and *Larsen* in further view of *Blann*, *Araneo* and *Defrees* and as evidenced by Maugeri et al. (Thrombosis and Haemostasis 72:450-456 (1994)) ("*Maugeri*") and Johnson et al. (J. Immunol. 159:4514-4523 (1997)) ("*Johnson*").

Claim 27 is directed to a method for inhibiting thrombus formation induced by LTC_4 in a subject comprising by identifying a subject at risk of thrombosis due to hypertension and administering to the subject a composition comprising an effective amount of soluble PSGL-1 protein or a fragment.

The Examiner acknowledges that *Cummings* and *Larsen* do not disclose the role of LTC_4 in thrombus formation and thrombotic conditions *per se*. The Examiner, however, contends that LTC_4 was a known thrombus-inducing agent in thrombus formation and thrombotic conditions, as evidenced by *Maugeri* and *Johnson*. (9/9/04 Office Action at page 8).

As discussed above, *Larsen* and *Cummings* do not provide or suggest treating or inhibiting thrombosis in a subject with hypertension. None of *Blann*, Araneo and *DeFrees* compensate for this deficiency as neither discuss administering a PSGL-1 protein for treating or inhibiting thrombosis in a subject with hypertension. *Maugeri* and *Johnson* do not compensate for this deficiency as they too fail to discuss treating or preventing thrombosis in a subject with hypertension.

Applicants note that both *Maugeri* and *Johnson* describe a mechanistic link between P-selectin and LTC_4. The Examiner postulates that LTC_4 was a known thrombus-inducing agent, and that the description of reduced production of LTC_4 (*Maugeri*) or inhibition of LTC_4-induced leukocyte rolling (*Johnson*) with the administration of an antibody to P-selectin would motivate a skilled artisan to administer PSGL-1 to treat patients with various thrombotic conditions. In contrast, *Maugeri* discloses that LTC_4 is a vascoconstrictor, and *Johnson* discloses the use of LTC_4 to induce an "acute" experimental model of inflammation. These references do not

disclose a thrombotic effect of P-selectin, let alone a thrombotic effect of PSGL-1. Applicants have previously argued against this rejection and believe it is improper. The addition of *Blann*, *Araneo* and *Defrees* does not compensate for the deficiencies in the rejection.

Therefore, the obviousness rejections combining *Cummings* and *Larsen* with these references should accordingly be withdrawn.

CONCLUSION

In view of the foregoing remarks, Applicants submit that this claimed invention is not anticipated or rendered obvious in view of the references cited against this application. Applicants therefore request the entry of this Amendment, the Examiner's reconsideration and the timely allowance of the pending claims. Should the Examiner feel that this application is not in condition for allowance, Applicants request that the Examiner contact the undersigned representative at 617-452-1606.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: December 9, 2004

By: Sapna Mehtani

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